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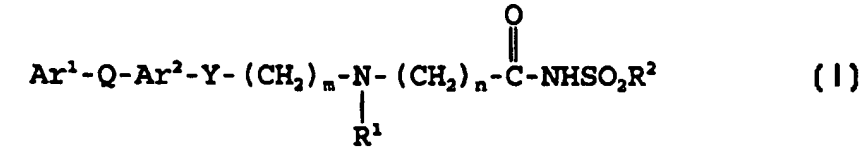
(57) Abstract

The present invention provides compounds having formula (I) and pharmaceutically acceptable salts and stereoisomers thereof that are useful in the treatment of inflammatory diseases which are mediated by LTB_4 production, such as psoriasis, ulcerative colitis, IBD, and asthma.



$$Ar^1\text{-}Q\text{-}Ar^2\text{-}Y\text{-}(CH_2)_m\text{-}N(R^1)\text{-}(CH_2)_n\text{-}C(=O)\text{-}NHSO_2R^2 \qquad (I)$$

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TITLE

LTA$_4$ HYDROLASE INHIBITORS

Field of the Invention

This invention relates generally to anti-inflammatory compounds and pharmaceutical compositions, and more particularly to anti-inflammatory compounds and compositions which are capable of inhibiting leukotriene A_4 hydrolase.

Background of the Invention

LTA_4 hydrolase is a requisite enzyme in the biosynthetic pathway leading to LTB_4 formation. LTB_4 is a proinflammatory compound. R. Lewis, et al., *N. Engl. J. Med.* 323, 645-655 (1990) have demonstrated that LTB_4 is a potent granulocyte agonist inducing chemotaxis, aggregation, degranulation, adherence and priming of inflammatory cells for induction by other agonists. Binding of LTB_4 to receptors is stereospecific with two distinct classes of binding sites. A. Lin, et al., *Prostaglandins* 28, 837-849 (1984). A high affinity site [$4\text{-}5\times10^{-10}$ M] mediates chemotaxis and chemokinesis while lower affinity sites [$0.6\text{-}5\times10^{-7}$ M] stimulate

granular secretion and oxidative burst. The LTB_4 receptor is associated with a GTP-binding protein that regulates affinity and transduces signals. T. Schepers, et al., *J. Biol. Chem.* 267, 159-165 (1992). Elevated LTB_4 levels have been reported for many diseases. Most prominently, elevated LTB_4 levels have been correlated to the pathology of inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis and in psoriasis. P. Sharon, et al., *Gastroent.* 86, 453-460; K. Lauritsen, et al., *Gastroent.* 95, 11-17 (1989); S. Brain, et al., *Br. J. Pharm.*, 83, 313-317 (1984). Other properties of LTB_4 which may contribute to disease processes are: stimulation of mucus secretion; stimulation of cytokine production; and the ability to act synergistically with other inflammatory mediators such as prostaglandins and cysteinyl leukotrienes thereby amplifying the inflammatory process.

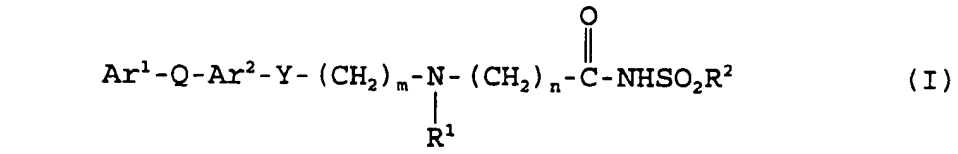
B. Samuelsson, et al., *J. Biol Chem.*, 264, 19469-19472 (1989) have shown that LTB_4 biosynthesis from arachidonic acid involves the action of 2 enzymes, 5-lipoxygenase [5-LO] and LTA_4 hydrolase. 5-LO transforms arachidonic acid to 5-HPETE and subsequent formation of LTA_4, which is an unstable allylic epoxide intermediate which is enzymatically hydrolyzed by LTA_4 hydrolase to form the dihydroxy acid LTB_4.

LTA_4 hydrolase is distinct from cytosolic and microsomal epoxide hydrolases based on strict substrate requirements, product formation [5(S),12(R) vs. 5(S),6(R)] for mouse liver cytosolic epoxide hydrolase, and lack of inhibition by inhibitors of cytosolic epoxide hydrolase. LTA_4 hydrolase appears to be ubiquitously distributed in mammalian tissues even in cell types that do not express 5-LO, suggesting the importance of transcellular metabolism of LTA_4. While peptidomimetic compounds such as bestatin and captopril

have been shown to exhibit LTA_4 hydrolase inhibitory activity, they are not able to satisfy the requirement of a small organic compound which is capable of cellular penetration. It would therefore be very advantageous to be able to provide low molecular weight inhibitors of LTB_4 biosynthesis which preferably exhibit oral activity in vivo at desirably low concentrations.

Summary of the Invention

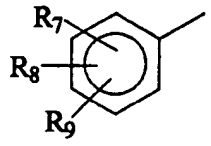
Applicants have now discovered that compounds of the formula (I):



$$Ar^1\text{-}Q\text{-}Ar^2\text{-}Y\text{-}(CH_2)_m\text{-}N(R^1)\text{-}(CH_2)_n\text{-}C(=O)\text{-}NHSO_2R^2 \qquad (I)$$

and pharmaceutically acceptable salts and stereoisomers thereof possess LTA_4 hydrolase inhibitor activity, wherein

Ar^1 is an aryl moiety selected from the group consisting of:

(i) 

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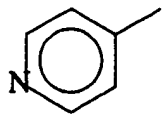
(ii) 

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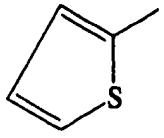
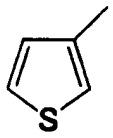
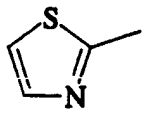
(iii) 

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of:

(i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

(ii) 2-, 4- or 5- thiazolyl,

(iii) 2-, 3- or 4-pyridinyl,

(iv) 2- or 3-thienyl, and

(v) 2- or 3-furyl;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

Y is selected from the group consisting of

(i) -O-,

(ii) -S-,

(iii) -NH-,

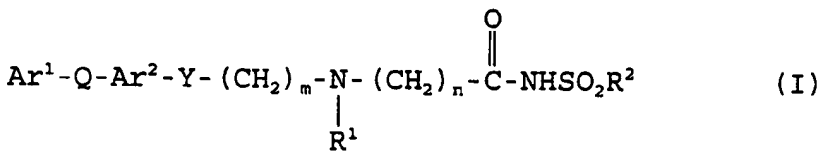
(iv) -S(O)-, and

(v) $-S(O_2)-$;

R^1 is hydrogen, lower alkyl, lower alkoxy or cyclic alkyl;
R^2 is lower alkyl or phenyl optionally substituted with lower alkyl or halogen or $NR^1(CH_2)$-$CONHSO_2R^2$ taken together forms pyrrolidino, piperidino, or piperazino substituted with $(CH_2)_p$-$CONHSO_2R^2$ and wherein the pyrrolidino, piperidino, or piperazino group is optionally substituted with one or two lower alkyl groups;
R^7, R^8, and R^9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2, NO_2 or OH;
m is an integer from 2 to 4;
n is an integer from 2 to 6; and
p is an integer from 1 to 3.

Detailed Description

In one of its embodiments, the present invention entails compounds of the formula I



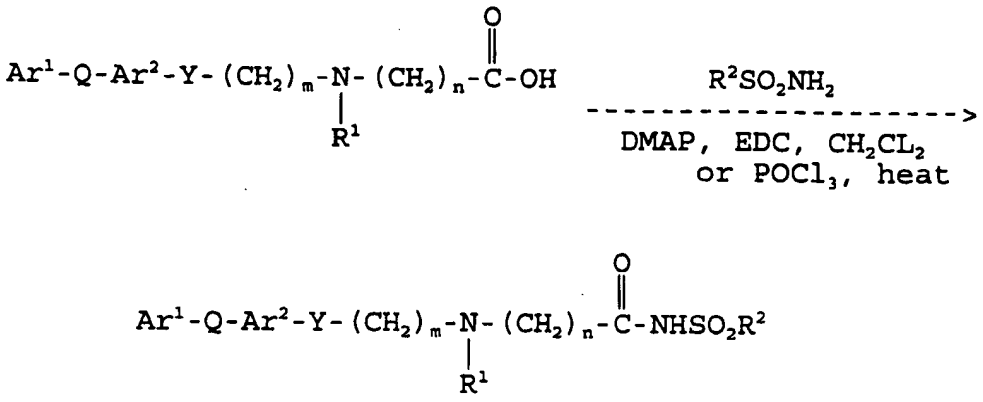
(I)

and pharmaceutically acceptable salts and stereoisomers thereof, wherein Ar^1, Ar^2, Q, Y, R^1, R^2, m and n are as defined above.

The compounds of the present invention can be prepared according to the methods disclosed and claimed in allowed U.S. Application No. 08/321,183, filed October 11, 1994. The disclosure of that application is hereby incorporated by reference into this specification to more fully describe the present invention.

In general, the compounds of the present invention are prepared by reacting the carboxylic acid compounds of U.S. Application No. 08/321,183 and an S-aryl- or S-

alkyl-sulfonamide under one of two sets of carboxylic acid activation conditions as follows:



The acid and the sulfonamide can be stirred with 4-dimethylaminopyridine (DMAP) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in dichloromethane (CH_2Cl_2). Alternatively, the acid and the sulfonamide can be heated neat with excess phosphorous oxychloride ($POCl_3$). These conditions are applicable to a broad range of carboxylic acids and sulfonamides. A more detailed description of the preparation of these compounds and preferred embodiements is provided below.

In another of its aspects, the invention entails a pharmaceutical composition comprising a pharmacologically effective amount of at least one of the compounds defined above and a pharmaceutically acceptable carrier.

In still another of its embodiments the present invention involves a method for treating a mammal exhibiting an LTB_4 mediated inflammatory condition comprising administering to the mammal a pharmacologically effective amount of at least one of the compounds defined above.

The term "lower alkyl" means straight or branched chain alkyl having 1 to 6 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl and the branched chain isomers thereof. The term "lower alkoxy" means straight or branched chain alkoxy having 1 to 6 carbon atoms such as methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the branched chain isomers thereof. The term "allyl" as used herein means the 1-propenyl radical, $-CH_2-CH_2=CH_2$. The term "halo" means fluoro, chloro, bromo, or iodo.

Included within the classes and subclasses of compounds embraced by this invention are isomeric forms of the described compounds including diastereoisomers, enantiomers and tautomeric forms of the described compounds. Pharmaceutically acceptable salts of such compounds are also included as well as pharmaceutically acceptable salts of such isomers and tautomers.

In the structures herein a bond drawn across a bond in a ring indicates that the bond can be to any available atom of the ring structure.

The expression "pharmaceutically acceptable salts" is intended to include those salts capable of being formed with the compounds of the present invention without materially altering the chemical structure or pharmacological properties thereof. Such salts can be inorganic and organic cations or acid addition salts, including, but not limited to, sodium, potassium, calcium, ammonium, alkylammonium, quaternary ammonium, triethanolamine, lysine, hydrochloride, hydrobromide, or others known to those of ordinary skill in the art. The foregoing salts are prepared in the conventional manner by neutralization of the compounds defined above with the desired base or acid.

The compounds of the present invention can be administered to a patient in such oral dosage forms as tablets, capsules, pills, powders, granules, elixirs or syrups, as well as aerosols for inhalation. Likewise, administration may be effected intravascularly, subcutaneously, or intramuscularly using dosage forms known to those of ordinary skill in the pharmaceutical arts. In general, the preferred form of administration is oral. An effective but non-toxic amount of the compound is employed in treatment. The dosage regimen utilizing the present compounds is selected in accordance with a variety of factors including the type, age, weight, sex and medical condition of the patient; the severity of the condition to be ameliorated; and the route of administration. A physician of ordinary skill can readily determine and prescribe a "pharmaceutically effective amount" of one or more of the compounds defined above, that is, the effective amount of the compound required to prevent, treat or arrest the progress of the condition. Dosages of the compounds of the present invention will range generally between 0.1 mg/kg/day to about 100 mg/kg/day and preferably between about 0.5 mg/kg/day to about 50 mg/kg/day when administered to patients suffering from allergic or hypersensitivity reactions or inflammation. The compounds may also be administered transdermally or topically to treat proliferative skin conditions such as psoriasis. The daily dosage may be administered in a single dose or in equal divided doses three to four times daily.

As used herein the phrase "LTA_4 hydrolase inhibitor" means a compound which is capable of exhibiting an IC_{50} of less than 1 mM in an in vitro assay employing 10 μg/ml of LTA_4 hydrolase enzyme (specific activity 600 nMoles LTB_4/min/mg of enzyme) in the presence of 25 μM substrate (LTA_4) in a total reaction volume of 100 μl.

In the pharmaceutical compositions and methods of the present invention, at least one of the active compounds defined above or a pharmaceutically acceptable salt thereof will typically be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier materials") suitably selected with respect to the intended form of administration and consistent with conventional pharmaceutical practices. For example, the pharmaceutical compositions of this invention can be administered to a subject as oral tablets, capsules, elixirs, syrups and the like. For oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like; for oral administration in liquid form, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as ethanol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintigrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Lubricants for use in these dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride and the like. Disintigrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum and the like.

By virtue of their activity as LTA_4 hydrolase inhibitors, the compounds of the invention are useful in treating inflammatory conditions mediated by LTB_4 production in mammals such as psoriasis, contact and

atropic dermatitis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, multiple sclerosis, ankylosing spondylitis, arthritis, asthma and the like. Similarly, the compounds of the invention can be used in preventing recurring inflammatory attacks. A physician or veterinarian of ordinary skill can readily determine whether a subject exhibits the inflammatory condition. A preferred utility relates to treatment of ulcerative colitis.

Examples of the compounds of the present invention include, but are not limited to, the following:

3-[Methyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(phenylsulfonyl)butanamide;

N-(Methylsulfonyl)-3-[methyl[3-[4-[(2-thienyl)-methyl]phenoxy]propyl]amino]propanamide;

3-[Ethyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide monohydrochloride;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrate;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(3-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

N-(methylsulfonyl)-3-[methyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

N-(phenylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide monohydrochloride;

N-(methylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

3-[(1-methylethyl[3-[4-[(3-thienyl)methyl]-phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[Cyclopropyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[(1,1-dimethylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[(1-methylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[(1-methylethyl)[3-[4-[(phenylmethyl)-phenoxy]propyl]amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

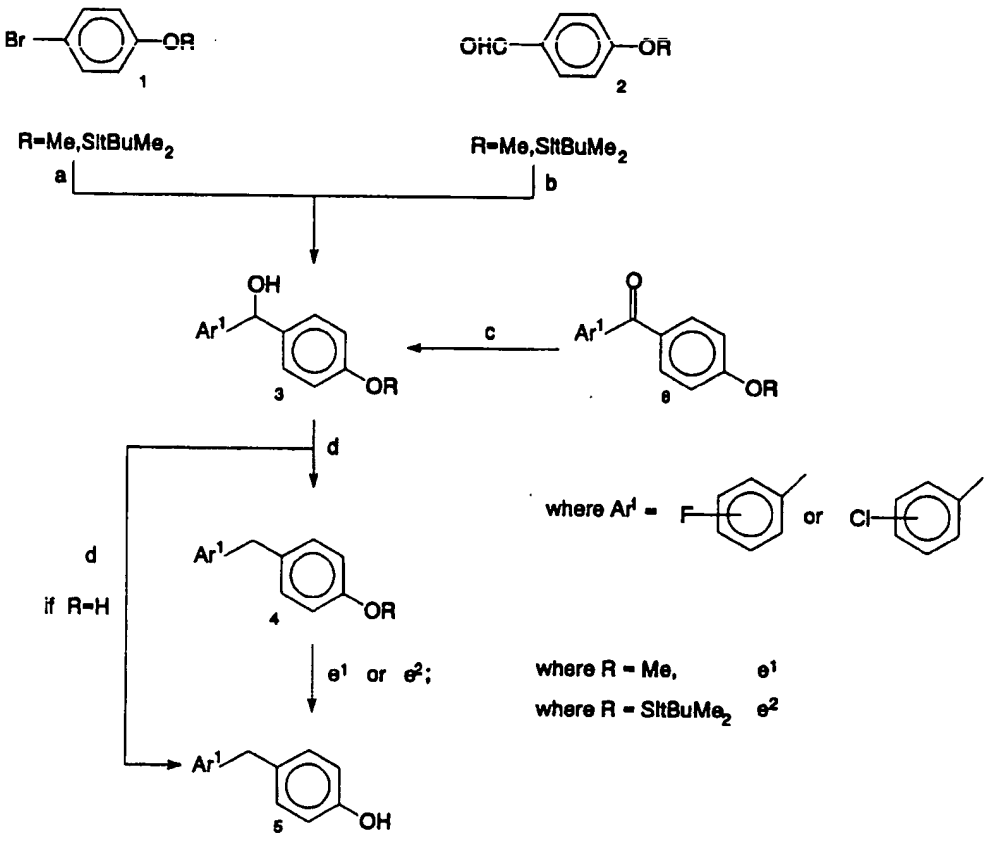
3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(phenylsulfonyl)-propanamide.

The compounds of the invention are prepared from readily available starting materials by any of the following alternate processes in a conventional manner. The following reaction schemes describe methods which can be employed for preparing the compounds of the invention, including starting materials, intermediates and reaction conditions. The following terms, as used herein, have the following definitions:

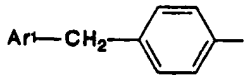
NMMO	N-methylmorpholine-N-oxide
Me	methyl
$SitBuMe_2$	t-butyldimethylsilyl
nBuLi	n-butyllithium
THF	tetrahydrofuran
Et_2O	diethyl ether
EtOH	ethyl alcohol
Pd/C	palladium on carbon
TFA	trifluoroacetic acid
Et_3SiH	triethylsilane
TBAF	tetrabutylammonium fluoride
DMF	dimethylformamide
nBu_4NBr	tetra-n-butylammonium bromide
TsCl	tosylchloride or p-toluenesulfonyl-chloride
TsO	tosylate or p-toluenesulfonate
MeOH	methyl alcohol
AcOH	acetic acid
Bn	benzyl
DEAD	diethylazodicarboxylate
Ph_3P	triphenylphosphine
MCPBA	metachloroperbenzoic acid
LAH	lithium aluminum hydride

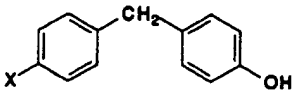
TsOH	tosic acid or p-toluenesulfonic acid
LDA	lithium diisopropylamide
DSC	disuccinylcarbonate
nBuOH	n-butyl alcohol
TFAA	trifluoroacetic anhydride
Me_3SnN_3	trimethyl-tin azide
TMS	trimethyl silyl
Ac_2O	acetic anhydride
Ac	acetate
EtOAc	ethyl acetate
Hep	heptane

Scheme 1

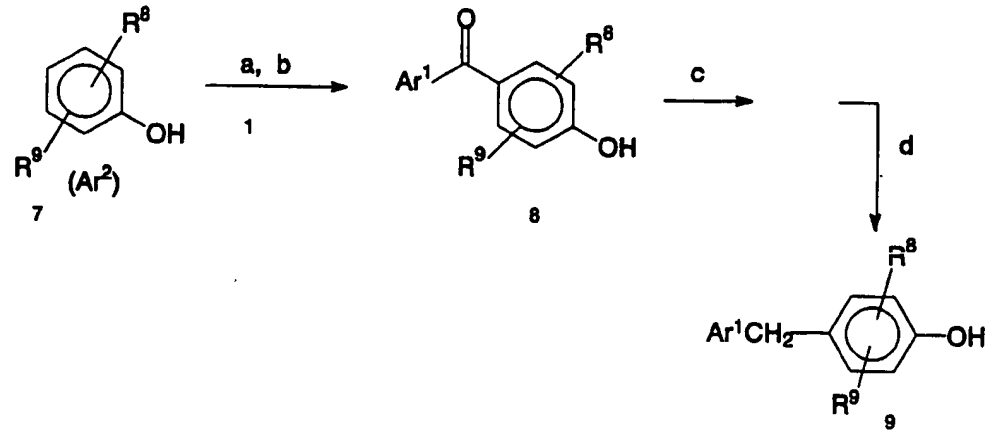


a) nBuLi, THF, -78°C; Ar^1CHO.
b) Ar^1Li or Ar^1MgBr, Et_2O, -78°C.
c) EtOH, $NaBH_4$.
d) EtOH, 4% Pd/C, H_2 or CH_2Cl_2, TFA, Et_3SiH
e^1) BBr_3, CH_2Cl_2, -78°C.
e^2) THF, TBAF.

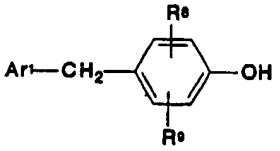
Scheme 1 shows methods for producing compounds of the formula  . Scheme 1 shows two related precursor compounds (**1**, **2**) which may be employed as a starting material. Compound **1** is an alkylated or silylated derivative of p-bromophenol. A convenient starting material **1** is 1-bromo-4-methoxyphenol (i.e., R is methyl). On the other hand, compound **1** may be readily provided by silylation of p-bromophenol with t-butyldiphenylsilyl chloride or other silylating agents (see, Example 2). In either event, compound **1** may be reacted with tert-butyl lithium in an ethereal solvent at low temperature, such as in THF at -78°C, and quenched with an arylaldehyde (Ar^1CHO) to yield compound **3**. Similarly, starting from compound **2**, a p-methoxybenzaldehyde or a silylated derivative of p-hydroxybenzaldehyde (see, Example 1) may be employed. Compound **2** may be reacted with an aryl lithium (Ar^1Li) or aryl magnesium bromide (Ar^1MgBr) to yield compound **3**. Regardless of which route is chosen, compound **3** is reduced, e.g., by hydrogenation over palladium on carbon or with triethylsilane, to provide compound **4**. Compound **4** is readily deprotected using TBAF in THF (desilylation) or using BBr_3 in methylene chloride at -78°C (dealkylation) to provide compound **5**.

Compounds **5** of the formula  , wherein X is halogen, preferably chloro or fluoro, are preferably provided by sodium borohydride reduction of a compound **6** to provide compound **3**, followed by hydrogenation as described above to afford compound **5**.

Scheme 2

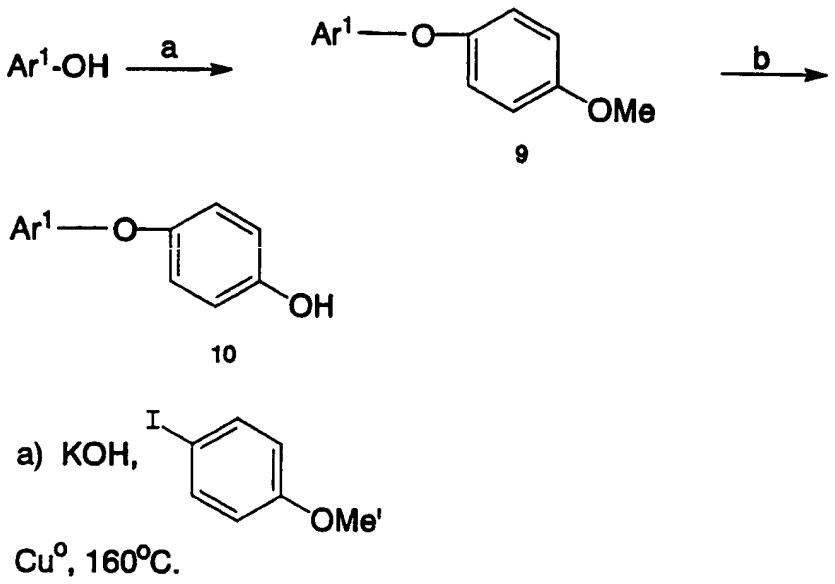


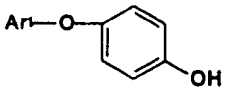
a) Ar^1COCl, CH_2Cl_2 Pyridine.
b) $AlCl_3$, 160°C, 5 min.
c) $NaBH_4$/EtOH.
d) TFA, CH_2Cl_2, Et_3SiH.

Scheme 2 depicts the preparation of compounds of formula 

, wherein R^8 and R^9 are as defined hereinbefore. In this reaction sequence, the substituted phenol **7** is reacted with a suitable aryloyl chloride to give the intermediate aryloyl ester (not shown) which is heated to a temperature of about 160°C in the presence of $AlCl_3$ to promote Fries rearrangement which affords the desired compound **8**, having the specifically substituted Ar^2 moiety. Compound **8** may be reduced utilizing the two-step reduction sequence (Scheme 1, steps (c) and (d)) to provide compound **9**.

Scheme 3

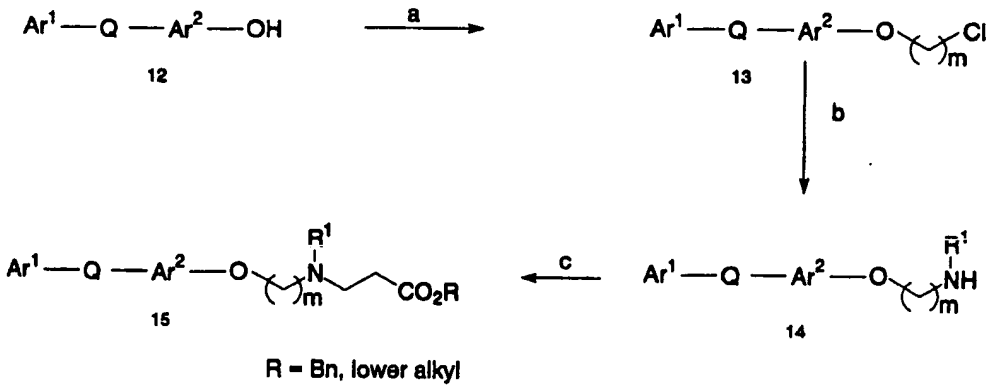


Scheme 3 shows a general method for the preparation of phenols of the formula 

wherein Ar^1 is a substituted phenol. Ar^1 may be any substituted arylphenol which is capable of reacting with 4-iodoanisole in an Ullman coupling reaction. See, A. Moroz, et al., *Russ. Chem. Rev.* 43, 679 (1974). The Ullman reaction is carried out conventionally in the presence of activated copper or copper iodide at a temperature of about 150°C to 200°C to give compound 9. A presently preferred substituted phenol for providing compounds of the present invention having a substituted Ar^1 moiety is 4-fluorophenol. Compound **10** may be

dealkylated using BBr_3 in methylene chloride at -78°C to yield compound **10**.

Scheme 4

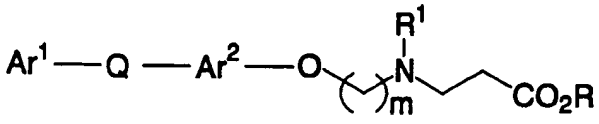


a) NaH, DMF, Cl(CH2)mBr

b) R^1NH_2, △

c) $CH_2=CHCO_2R$ R = Bn, lower alkyl

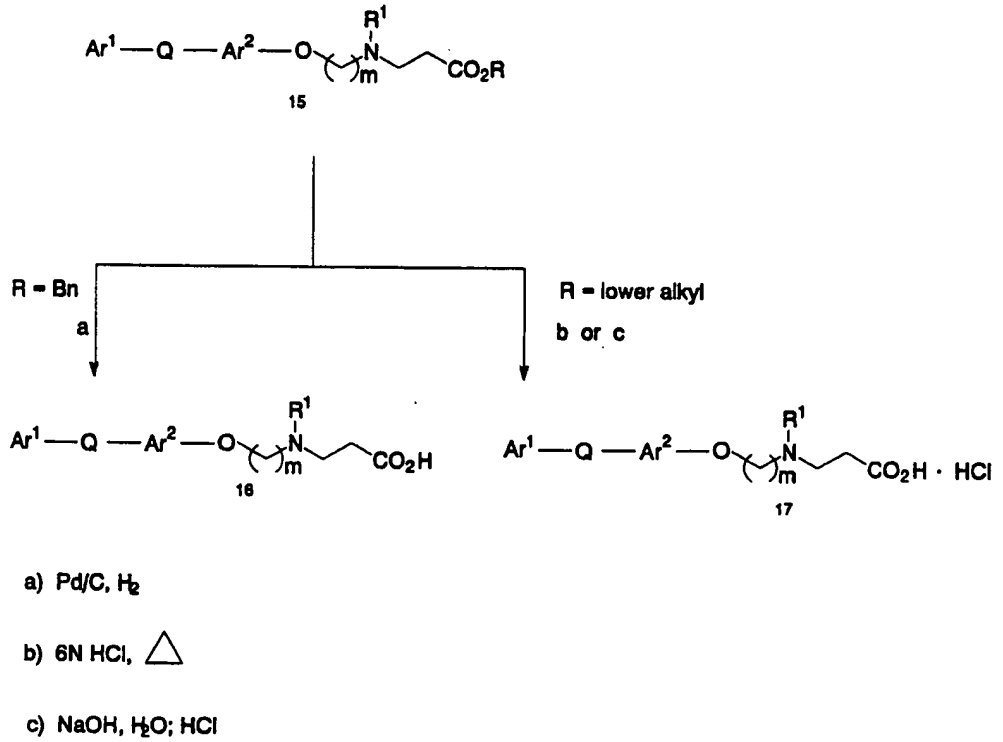
Scheme 4 depicts a general method for the preparation of carboxylic esters of the formula



Compound **12** is reacted with $Cl(CH_2)_mBr$ (wherein m is 2-4) in the presence of DMF and NaH to provide compound **13**. Compound **13** is heated ("Δ") with an amine of the formula R^1NH_2, wherein R^1 is as defined hereinbefore with reference to compounds of formula I, to give compound **14**. Compound **14** is reacted with

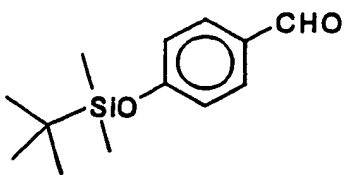
benzylacrylate ester or an alkylacrylate ester to afford compound **15**.

Scheme 5



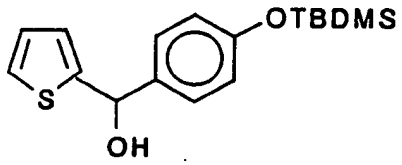
Scheme 5 shows the conversion of compound **15** which comprises an ester moiety to the corresponding acid **16** or hydrochloride **17** via one of three reactions: (1) basic hydrolysis (route c); (2) acidic hydrolysis (route b, "Δ" referring to elevated temperature), which is preferred where R is a lower alkyl; or (3) hydrogenolysis over palladium on carbon in EtOH (route a), which is especially preferred where R is benzyl.

Example 1



To a stirred solution of 4-hydroxybenzaldehyde (12.39 , 0.1 mol, Aldrich) in DMF (50 mL) was added t-butyldimethylsilyl chloride (18.1 g, 0.12 mol) and imidazole (17 g, 0.25 mol). The mixture was stirred at room temperature for 16 hours, and diluted with pentane (200 mL). The organic layer was washed with water (3X) and brine, dried over Na_2SO_4 and concentrated in vacuo to give 25 g of the title compound as yellow oil. The resulting product had a ^1H NMR (300 MHz) spectrum consistent with proposed structure. M+ = 236.

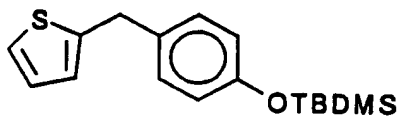
Example 2



2-Bromothiophene (815 mg, 5 mmols, Aldrich) was dissolved in dry THF (20 mL) and cooled to -78°C. n-Butyllithium (3.4 mL of 1.6M solution) was added and the reaction was stirred for 2 hours under Argon. The aldehyde of Example 1 (1.18 g, 5 mmols) in THF (1 mL) was added and reaction mixture allowed to warm to room temperature over 1.5 hours. Water was added and the solution was extracted with ethyl acetate (3 X 30 mL). The combined organic layers were washed with brine,

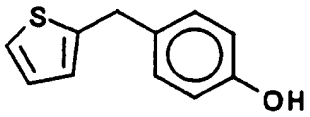
dried over Na_2SO4, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using EtOAC/Heptane (20/80) as eluant to give 160 mg of compound as yellow oil. The resulting product had a ^1H NMR (300 MHz) spectrum consistent with proposed structure.

Example 3



The product of Example 2 (0.5 mmol) was mixed with Et_3SiH (0.5 mL, Aldrich) and TFA (0.4mL) and stirred at room temperature for 6 hours under Argon. The reaction mixture was concentrated and the residue obtained was basified with 10% aqueous NaOH solution. The reaction solution was extracted with ether (3 X 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated to give 160 mg product. The resulting product was fully characterized in the next step.

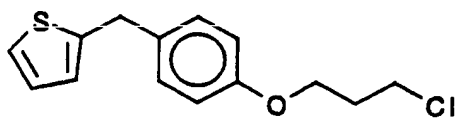
Example 4



The product of Example 3 was treated with tetrabutylammonium fluoride (2.5 mL of 1M solution, Aldrich) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, the residue obtained was treated with water and ether. The organic layer was separated and

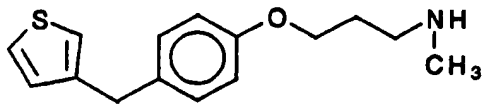
washed two times with water and brine, dried over Na_2SO_4 and concentrated in vacuo to give 90 mg of the title compound as yellow oil. The resulting product was fully characterized in the next step.

Example 5



To the compound of Example 4 (1.84 g) in 50 ml dimethylformamide (DMF) was added sodium hydride (60% dispersion in mineral oil) 0.5 g (Aldrich) portionwise at room temperature during 15 min. The reaction mixture was stirred for 1/2 hr and 1.57 g of 1-bromo-3-chloro propane (Aldrich) in 10 ml of DMF was added dropwise during 10 min and the mixture was stirred at room temperature overnight. Diethyl ether 100 ml and water 3 ml was added to the reaction mixture and the organic phase was further washed with H_2O (10 ml x 2), dried, filtered, and the solvent removed in vacuo. The organic material was chromatographed over silica gel using 5% EtOAc in hexane and gave the title compound.

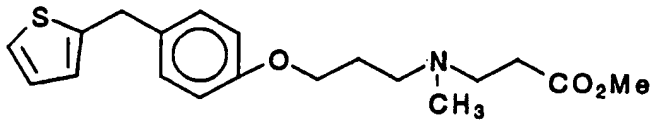
Example 6



To a stirred solution of methylamine (40% solution in H_2O, Aldrich) (13.7 mL, 180 mmol) was added a solution of Example 2 (0.47 g, 1.8 mmol, in CH_3CN 5 mL). The resulting mixture was heated to 45-50°C for 4-5 hours and then allowed to stir at room temperature for 15

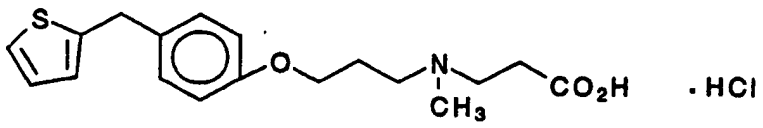
hours. The reaction was concentrated in vacuo and the aqueous residue extracted with EtOAc (2 x 15 mL). The organic layers were combined and acidified with 1N HCl to pH 1 at 0°C. A white precipitate was formed, and the solid was collected by vacuum filtration. The solid was washed with 1N HCl, followed by hexane to afford 0.35 g salt. The solid was dissolved in 10% NaOH (30 mL) and extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give the free amine as a clear colorless oil (0.3 g).

Example 7



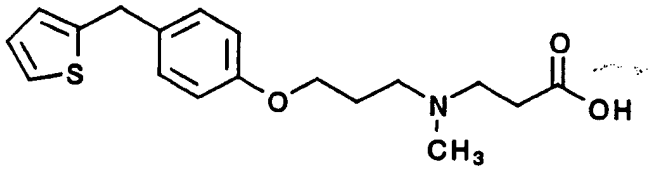
To a stirred solution of the compound of example 6 (0.30 g, 1.1 mmol in CH_2Cl_2 6 mL) was added methyl acrylate (Aldrich, 0.13 mL, 1.5 mmol) at room temperature. The reaction was allowed to stir at room temperature for 17 hours, and then concentrated under a stream of nitrogen gas. The residue was purified by column chromatography using 10% MeOH/CH_2Cl_2 as eluant to afford 0.32 g of the title compound as a clear colorless oil. The resulting product had the following properties: Analysis calc'd for $C_{19}H_{25}NO_3S$: C, 65.58; H, 7.25; N, 4.03. Found: C, 65.38; H, 7.30; N, 3.95.

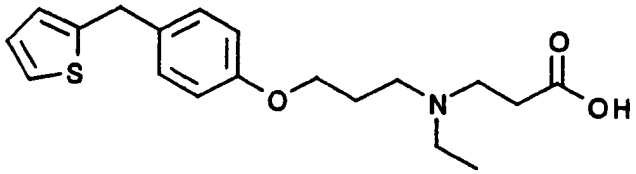
Example 8

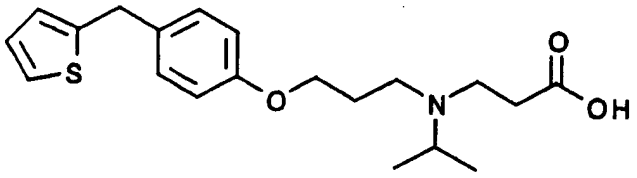


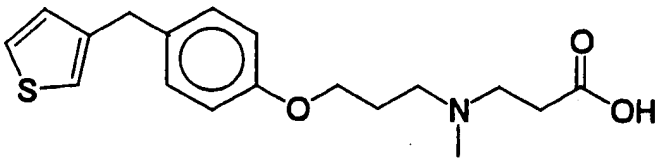
A solution of the compound of Example 7 (80 mg, 0.23 mmol) in 6 N HCl (1 mL) was heated to 70°C for 4 hours, then concentrated in vacuo to give a white solid. The solid was slurried with Et_2O and collected by vacuum filtration to give 110 mg of the title compound. The resulting product had the following properties: Analysis calc'd for $C_{18}H_{24}NO_3SCl$ 1.3 H_2O: C, 56.30; H, 6.01; N, 3.46. Found: C, 56.05; H, 6.22; N, 3.37.

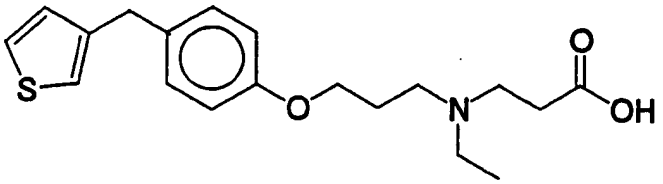
The following carboxylic acids are referred to by number in Examples 9 through 29:

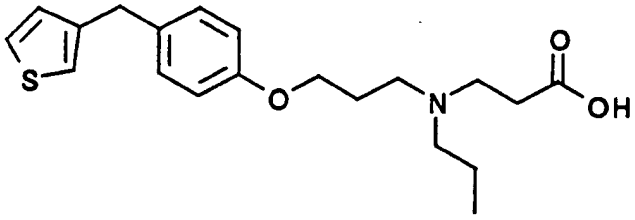
1. 

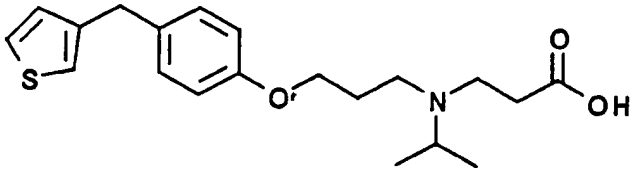
2. 

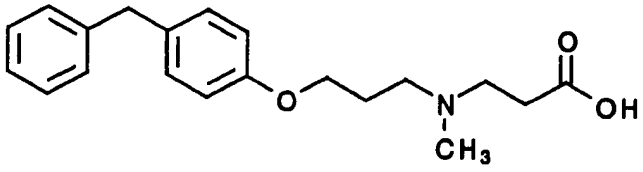
3. 

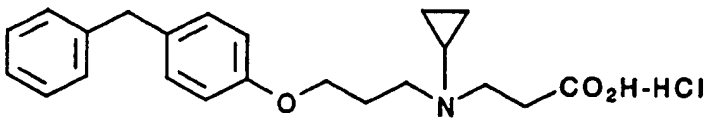
4. 

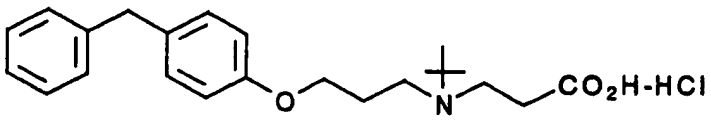
5. 

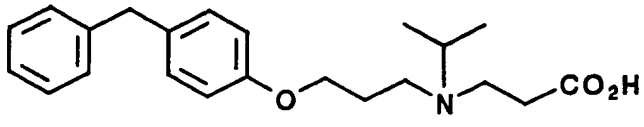
6. 

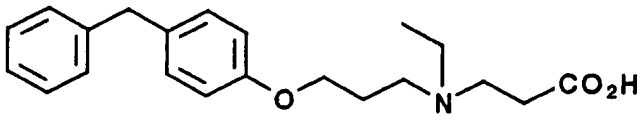
7. 

8. 

9. 

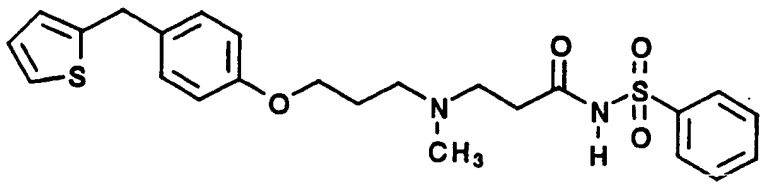
10. 

11. 

12. 

Example 9

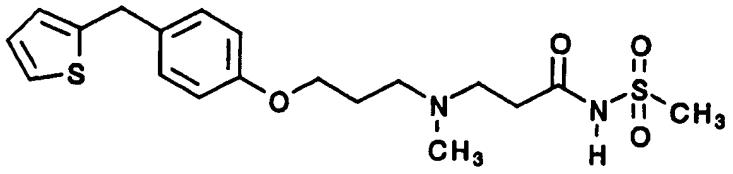
3-[Methyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(phenylsulfonyl)butanamide



To a mixture of carboxylic acid 1 (300 mg, 0.81 mmol) in CH_2Cl_2 (2 mL) was added benzenesulfonamide (130 mg. 0.81 mmol) and dimethylaminopyridine (DMAP, 128 mg. 1.1 mmol). The solids went into solution and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 160 mg, 0.81 mmol) was added. The reaction was stirred at room temperature for 18 hours and then partitioned between CH_2Cl_2 and 10% aqeous HCl. The aqueous solution was extracted with CH_2Cl_2. The combined organic solution was dried (Na_2SO_2) and concentrated in vacuo. The residue was chromatographed on silica (85:14:1 CH_2Cl_2:MeOH:NH_4OH) to give the desired compound (29 mg,8%) as a gummy solid. Anal. calc'd for $C_{24}H_{28}N_2O_4S_2$+0.5 H_2O: C, 59.85; H, 6.07; N, 5.81. Found: C, 60.03; H, 6.11; N, 5.82.

Example 10

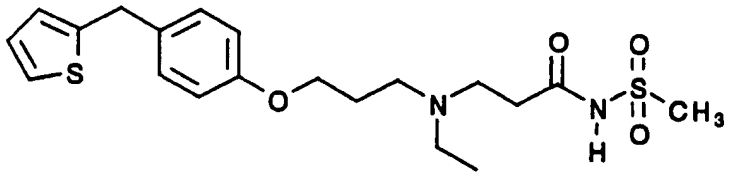
N-(Methylsulfonyl)-3-[methyl[3-[4-[(2-thienyl)-methyl]phenoxy]propyl]amino]propanamide



A mixture of carboxylic acid 1 (300 mg, 0.81 mmol), methanesulfonamide (77 mg, 0.81 mmol) and phosphorous oxychloride ($POCl_3$, 0.25 ml, 2.6 mmol) was heated at 90°C for 3 hours. The reaction solution was cooled, diluted with CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2. The combined organic solution was dried (Na_4SO_4) and concentrated in vacuo. The residue was chromatographed on silica (85:14:1 CH_2Cl_2:MeOH:NH_4OH) to give the desired compound (85 mg,26%) as a viscous oil. Anal. calc'd for $C_{19}H_{26}N_2O_4S_2$+0.5 H_2O: C, 54.38; H, 6.48; N, 6.67. Found: C, 54.27; H, 6.59; N, 6.54.

Example 11

3-[Ethyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride

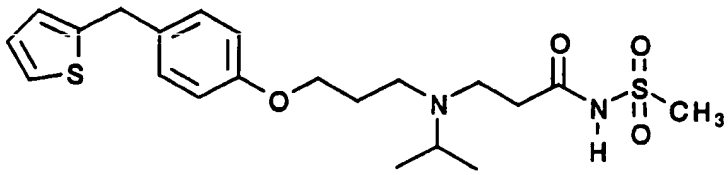


The method of Example 10 was repeated starting with carboxylic acid 2 (130 mg, 0.34 mmol), methanesulfonamide (33 mg, 0.34 mmol) and phosphorus oxychloride (0.10 mL, 1.1 mmol) which formed the desired product (48 mg, 33%) as a crystalline solid, mp

103-4°C. Anal. calc'd for $C_{20}H_{28}N_2O_4S_2$+1.0 HCl: C, 52.10; H, 6.34; N, 6.07. Found: C, 52.33; H, 6.42; N, 6.10.

Example 12

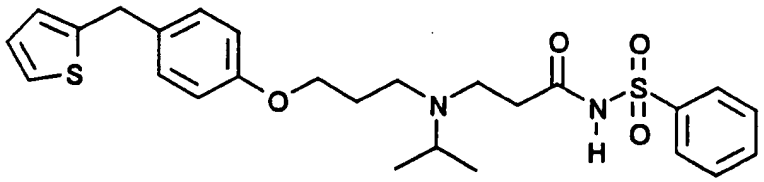
3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide monohydrochloride



The method of Example 10 was repeated starting with carboxylic acid 3 (160 mg, 0.4 mmol), methanesulfonamide (38 mg, 0.4 mmol) and phosphorus oxychloride (0.12 mL, 1.3 mmol) which formed the desired product (62 mg, 37%) as a viscous oil. Anal. calc'd for $C_{21}H_{30}N_2O_4S_2$+1.0 HCl: C, 53.09; H, 6.58; N, 5.89. Found: C, 52.90; H, 6.68; N, 5.83.

Example 13

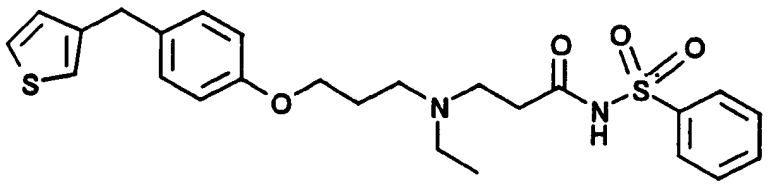
3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide, monohydrochloride



The method of Example 10 was repeated starting with carboxylic acid 3 (170 mg, 0.42 mmol), benzenesulfonamide (67 mg, 0.42 mmol) and phosphorus oxychloride (0.13 mL, 1.35 mmol) which formed the desired product (80 mg, 37%) as a viscous oil.

Example 14

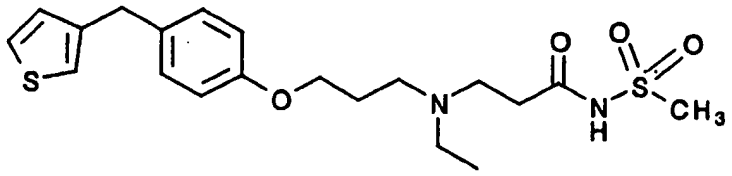
3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrate



Carboxylic acid 5 (290 mg, 0.83 mmol) was dissolved in 10 mL of CH_2Cl_2 and benzensulfonamide, EDC and DMAP were added. The reaction mixture was stirred under nitrogen overnight and the reaction mixture was quenched with water and extracted 3 times with CH_2Cl_2. The organic layers were dried over anhydrous $MgSO_4$ and concentrated to the crude product which was purified by flash chromatography on silica gel using 20/79/1 $EtOH/CH_2Cl_2/NH_4OH$ as eluent to give the product (170 mg). Anal. calc'd for $C_{25}H_{30}N_2S_2O_4 \bullet H_2O$: C, 59.50; H, 6.39; N, 5.55. Found: C, 59.18; H, 6.04; N, 5.64.

Example 15

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride

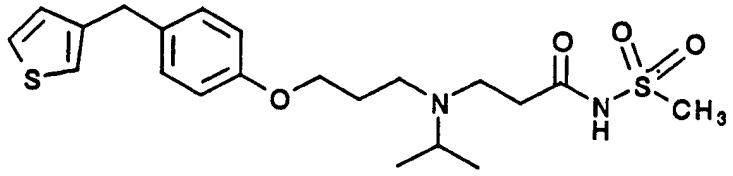


Carboxylic acid 5 (478 mg, 1.38 mmol) was dissolved in 10 ml CH_2Cl_2, and methanesulfonamide (131 mg, 1.38 mmol), EDC (272 mg, 1.31 mmol) and DMAP (219 mg, 1.79 mmol) were added. The reaction mixture was stirred under nitrogen overnight. The reaction mixture was partitioned between CH_2Cl_2 and water and the organic layer was dried over $MgSO_4$ and concentrated in vacuo to

give an oil which was purified by chromatography using 15/84/1 EtOH/CH_2Cl_2/NH_4OH as eluent to give the desired product (59 mg). Anal. calc'd for $C_{20}H_{28}N_2O_4S_2 \bullet HCl$: C, 52.10; H, 6.34; N, 6.08. Found: C, 51.82; H, 6.38; N, 5.73.

Example 16

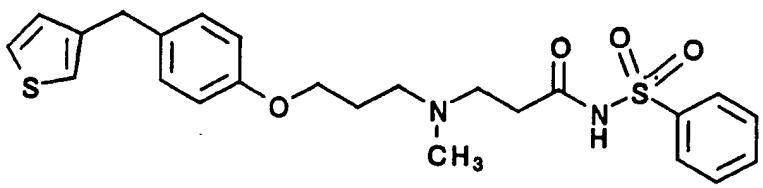
3-[(1-methylethyl) [3-[4-[(3-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide



Carboxylic acid 7 (320 mg, 0.88 mmol), methanesulfonamide (84.3 mg, 0.88 mmol) and 2 mL of phosphorus oxychloride ($POCl_3$) were heated at 90°C for 5 h. The reaction mixture was quenched with water and neutralized with aq. Na_2CO_3. The mixture was extracted with CH_2Cl_2 and the organic layer separated, dried over $MgSO_4$ and concentrated to give an oil which was purified by chromatography using 4/95/1 EtOH/CH_2Cl_2/NH_4OH as eluent to give 138 mg of product. Anal. calc'd for $C_{21}H_{30}N_2O_4S_2.0.8$ HCl: C, 53.92; H, 6.64; N, 5.99. Found: C, 53.74; H, 6.85; N, 5.78.

Example 17

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride

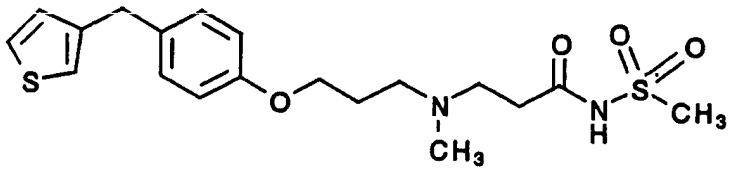


Carboxylic acid 4 (300 mg, 0.9 mmol) was converted to the sulfonamide using the EDC conditions as in Example

15 to give 150 mg of product: Anal. calc'd for $C_{24}H_{28}N_2O_4S_2 \cdot 0.5\ H_2O$: C, 59.85; H, 6.07; N, 5.80. Found: C, 59.64; H, 5.94; N, 5.80.

Example 18

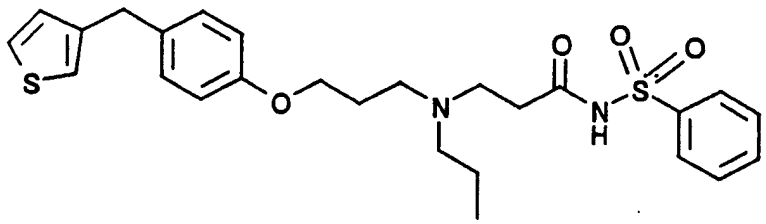
N-(methylsulfonyl)-3-[methyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide



Carboxylic acid 4 (389 mg, 1.17 mmol) was converted to the sulfonamide using the $POCl_3$ conditions as in Example 16 to give 101 mg of product; Anal. calc'd for $C_{19}H_{26}N_2O_4S_2 \bullet 0.4\ H_2O$; C, 54.63; H, 6,47; N, 6.71. Found: C, 54.56; H, 6.66; N, 6.76.

Example 19

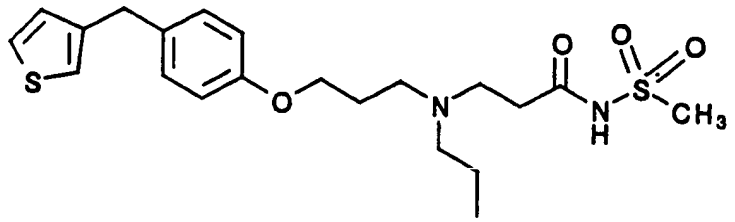
N-(phenylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide monohydrochloride



Carboxylic acid 6 (304 mg, 0.81 mmol) was converted to the sulfonamide using the $POCl_3$ conditions as in Example 16 to give 83 mg of desired product: Anal. calc'd for $C_{21}H_{30}N_2O_4S_2 \bullet 0.8\ H_2O$: C, 55.68; H, 7.03; N, 6.18. Found: C, 55.43; H, 7.08; N, 6.04.

Example 20

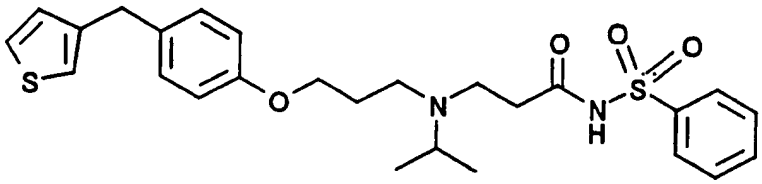
N-(methylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide



Carboxylic acid 6 (200mg, 0.532 mmol) was converted to the sulfonamide using the $POCl_3$ conditions as in Example 16 to give 80 mg of desired product; Anal. calc'd for $C_{26}H_{33}N_2O_4S_2Cl \bullet 0.1\ H_2O$: C, 57.94; H, 6.21; N, 5.20. Found: C, 57.64; H, 5.97; N, 5.06.

Example 21

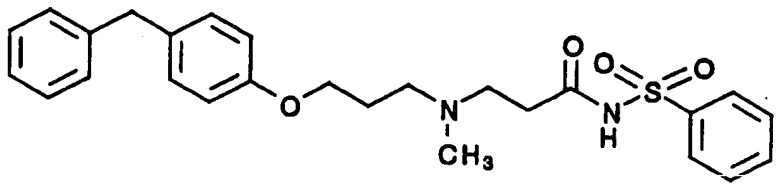
3-[(1-methylethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide



Carboxylic acid 7 (304 mg, 0.84 mmol) was converted to the sulfonamide using the EDC conditions as in Example 15 to give 40 mg of product; Anal. calc'd for $C_{26}H_{32}N_2O_4S_2 \bullet 0.3\ H_2O$: C, 61.71; H, 6.49; N, 5.54. Found: C, 61.35; H, 6.03; N, 5.39.

Example 22

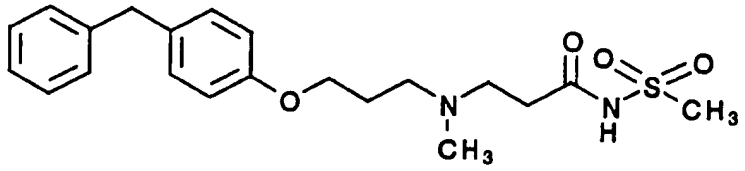
3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide



Carboxylic acid 8 (500mg, 1.37 mmol) was converted to the phenylsulfonamide using the EDC conditions as in Example 15 to give 130 mg of product: Anal. calc'd for $C_{26}H_{30}N_2SO_4$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.68; H, 6.46; N, 5.92.

Example 23

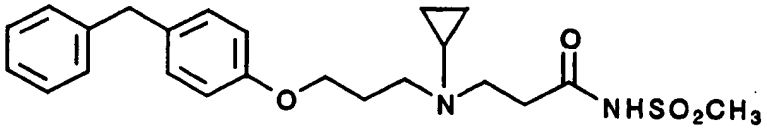
3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide



Carboxylic acid 8 (500mg, 1.37 mmol) was converted to the methylsulfonamide using the EDC conditions as in Example 15 to give 150 mg of product; Anal. calc'd for $C_{21}H_{28}N_2O_4S \bullet 0.9\ H_2O$: C, 59.95; H 7.14; N, 6.66. Found: C, 59.58; H, 6.99; N, 6.47.

Example 24

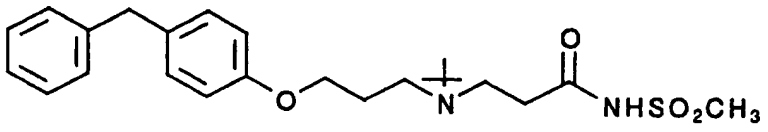
3-[Cyclopropyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide



To the carboxylic acid 9 (391 mg) was added phosphorus oxychloride (0.4 mL) and methanesulfonamide (110 mg) and the mixture heated to 90°C for 2 h. The mixture was cooled and extracted with 20 mL of ethyl acetate. The organic extract was concentrated and chromatographed over silica gel using 30:70:1 - EtOH:EtOAc:NH_4OH to give the desired product, 0.2 g. Anal. Calc'd for $C_{23}H_{30}N_2O_4S \bullet 0.8H_2O$: C, 62.08; H, 7.16; N, 6.30. Found: C, 61.83; H, 7.18; N, 6.21.

Example 25

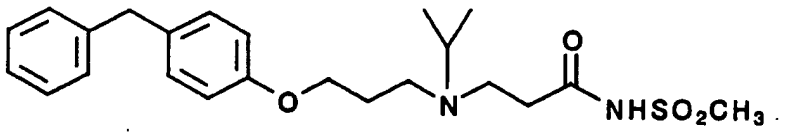
3-[(1,1-dimethylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide



To carboxylic acid 10 (40 mg) was added $POCl_3$ (0.05 mL), methanesulfonamide (10 mg) and the mixture heated to 90°C as described in Example **16**. The reaction mixture was chromatographed over silica gel using 30:70:1 EtOH:EtOAc:NH_4OH, 1H NMR (MeOD) δ 1.51 (s, 9H), 2.26-2.40 (m, 2H), 2.7-2.75 (m, 2H), 3.08 (s,3H), 3.35-3.42 (m,4H), 3.92 (s, 2H), 4.05-4.12 (m, 2H), 6.82-6.87 (m, 2H), 7.09-7.31 (m, 7H) 7.57 (s,1H).

Example 26

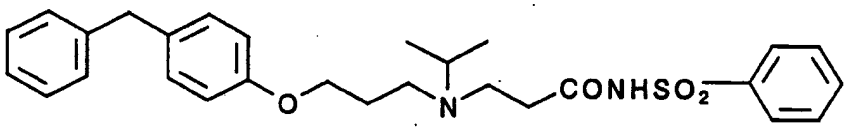
3-[(1-methylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide



Carboxylic acid 11 was converted to the methylsulfonamide using the $POCl_3$ procedure described in Example 25.

Example 27

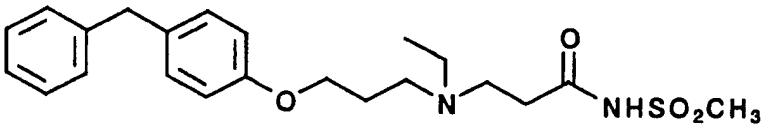
3-[(1-methylethyl)[3-[4-[(phenylmethyl)-phenoxy]propyl]amino]-N-(methylsulfonyl)-propanamide



Carboxylic acid 11 (760 mg) was converted to the desired product using the EDC/DMAP procedure as in Example 15 to give the sulfonamide as a white solid.

Example 28

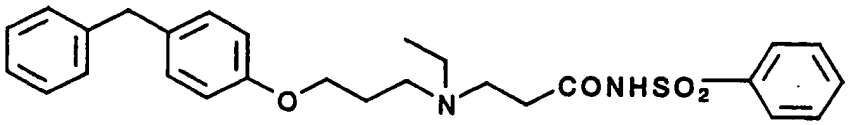
3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide



Carboxylic acid 12 (760 mg) was converted to the methylsulfonamide using the $POCl_3$ procedure as in Example 25 to give 350 mg of desired material.

Example 29

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(phenylsulfonyl)-propanamide



Carboxylic acid 12 (670 mg) was converted to the phenylsulfonamide using the EDC/DMAP procedure as in Example 15 to give 0.3 g of sulfonamide.

LTA Hydrolase Methods

The following Table presents data demonstrating the pharmacological activity of the LTA hydrolase inhibitors of the present invention. One or more of three different assays, (1) an in vitro LTA hydrolase enzyme assay, (2) a human whole blood assay utilizing calcium ionophore stimulation, and (3) a murine ex vivo assay utilizing calcium ionophore stimulation were employed to determine the level of LTA hydrolase inhibitor activity.

Recombinant Human LTA Hydrolase Assay for LTA Hydrolase Inhibitor Activity

Compounds of the present invention were tested for LTA hydrolase inhibitor activity against recombinant human LTA hydrolase (rhLTAH). Recombinant human LTA hydrolase-encoding vectors were prepared and used to express rhLTAH essentially as described by J. Gierse, et al., *Protein Expression and Purification*, 4, 358-366 (1993). Briefly, LTA hydrolase encoding DNA was amplified by polymerase chain reaction using a pair of oligonucleotide primers based on the nucleotide sequence from the 5'-end, and the complement of the 3'-

end, of the coding region of the LTA hydrolase gene, the nucleotide sequence of which gene is known. (See, C. Funk, et al., Proc. Natl. Acad. Sci. USA 84, 6677-6681 (1987)). A λgt11 human placental cDNA library (Clonetech, Palo Alto, CA) provided the nucleic acid template. The LTA hydrolase encoding region had a length of about 1.9 kb. The amplified 1.9 kb DNA was isolated and cloned into the genomic baculovirus, *Autographa californica* nuclear polyderosis virus (AcNPC) DNA, and the baculovirus expression vector was transfected into Spodoptera frugiperda Sf-9 cells employing the calcium phosphate co-precipitation method (see, M. Summers, et al., Tex. Agric. Exp. Stn. Bull. 1555, 1-57 (1987). Recombinant LTA_4 hydrolase enzyme was purified from the transfected Sf-9 cells essentially as described by J. Gierse, et al., supra.

One or more predetermined amounts of a compound of the invention were incubated in assay buffer (0.1 M potassium phosphate, 5 mg/ml fatty acid free BSA, 10% DMSO, pH 7.4) for 10 minutes at room temperature with 250 ng of recombinant $hLTA_4H$ to allow binding, if any, between the enzyme and inhibitor. The stock enzyme solution was 1 mg/m. LTA_4 hydrolase, 50 mM Tris, pH 8.0, 150 mM NaCl, 2.5 mM beta-mercaptoethanol, 50% glycerol. The specific activity of the enzyme was about 650 nMoles/min/mg. LTA_4 (i.e., substrate) was prepared from the methyl ester of LTA_4 (Biomol, Inc., Plymouth Meeting, PA) by treating the methyl ester with 30 molar equivalents of LiOH at room temperature for 18 hours. The LTA_4 substrate in its free acid form was kept frozen at -80°C until needed. LTA_4 (free acid) was thawed and diluted in assay buffer (minus DMSO) to a concentration of 350 ng/ml and 25 μl (8ng) of LTA_4 substrate was added to the reaction mixture (total volume of reaction mixture = 200 μl at time zero. Each reaction was carried out at room temperature for 10

minutes. The reaction was stopped by diluting 25 μl of the reaction mixture with 500 μl of the assay buffer without DMSO. LTA_4 was quantified in the diluted sample by a commercially available enzyme-linked immunoassay [Caymen Chemical Col. Ann Arbor, MI] using the method recommended in the manufacturer's instructions and compared to the amount of LTA_4 produced in a negative control (i.e., essentially identical conditions except without addition of an inhibitor compound). The IC_{50} was routinely calculated from the data produced.

LTB_4 and Thromboxane Production by Calcium Ionophore Stimulated Human Blood for LTB_4 Hydrolase Inhibitor Activity

Human blood, collected in heparin-containing Vacutainer tubes, was diluted 1:4 with RPMI-1640 media and 200 μl of the diluted blood was added into each of a 96-well microtiter plate. One or more concentrations of the leukotriene A_4 hydrolase inhibitor compounds being tested were prepared (diluted in DMSO) and 2 μl added and gently mixed with the diluted whole blood. After incubating for 15 minutes at 37°C in a humidified incubator, calcium ionophore A13187 (Sigma Chemical Co., St. Louis, MO) was added to a final concentration of 20 mcg/ml and the incubation continued under the same conditions for an additional 10 minutes to allow LTB_4 formation. The reaction was terminated by centrifugation (833 g, 10 minutes at 4°C) and supernatant were analyzed for LTB_4 and thromboxane by commercially available enzyme-linked immunoassays (Caymen Chemical Co., Ann Arbor, MI) according to the manufacturer's instructions. The IC_{50} of each test compound was determined from the amount of inhibition of LTB_4 production as compared to an essentially identical assay in which no inhibitor compound was present.

Ex Vivo LTB_4 and Thromboxane Production by Calcium Ionophore Stimulated Mouse Blood for LTB_4 Hydrolase Inhibitor Activity

Leukotriene A_4 hydrolase inhibitor compounds of the present invention were diluted to a predetermined concentration in phosphate buffered saline containing 2% DMSO and 1% Tween 80. The compounds were administered by oral gavage to adult male outbred mice weighing approximately 20-30 gm at a dose of 10 mg/kg body weight. (Compounds given at a dose of 50 mg/kg body weight are designated in following Table by the symbol, *) Sixty (60) minutes after administration of an LTA_4 inhibitor compound of the invention, blood was collected (into heparin-containing tubes) from the retroorbital sinus. The heparinized blood was added to the wells of a microtiter plate along with an equal volume of RPMI-1640 media, and calcium ionophore A23187 was added to a final concentration of 20 mcg/ml. The mixture was incubated for 10 minutes at 37°C in a humidified incubator. The reaction was terminated by centrifugation (833 g. 10 minutes at 4°C). Supernatant were analyzed for LTB_4 and thromboxane by commercially available enzyme-linked immunoassays [Caymen Chemical Co., Ann Arbor, MI] in accordance with the manufacturer's instructions. The percent inhibition was determined by comparison to animals treated identically except that the solution administered by oral gavage was devoid of inhibitor compound.

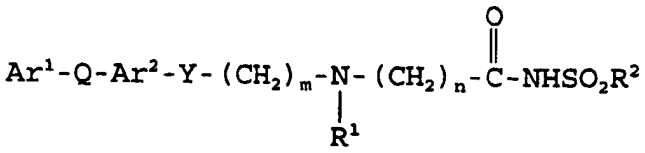
LTA_4 HYDROLASE INHIBITOR ACTIVITY

Ex.#	Recombinant Human LTA_4 Hydrolase Assay IC_{50} (μM) LTA_4	Inhibition of Calcium Ionophore-induced LTB_4 Production in Human Blood IC_{50} (μM) HWB	Murine Ex Vivo LTB_4 Inhibition %I LTB_4/at 1 hour after administration of 10mg/kg (* indicates administration of 50 mg/kg)
9	< 0.0005	0.079	87
10	0.0005	0.061	93
11	0.033	0.066	86
12	0.012	0.08	68
13	0.0023	0.04	50
14	0.011	0.082	87
15	0.43	0.23	79
16	0.45	0.2	85
17	0.0005	0.13	93
18	0.02	0.19	94
19	0.09	0.075	45
20	0.15	0.15	56
21	0.09	0.15	60
22	0.001	0.075	94
23	0.0013	0.07	100
24	2.16	2.71	-
25	0.1	0.11	45
26	0.16	0.22	81
27	0.047	0.1	44
28	0.54	0.18	89
29	0.079	0.13	65

"-" means Not Determined

What is claimed is

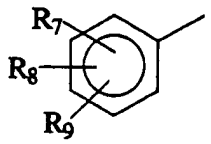
1. A compound having the structure:

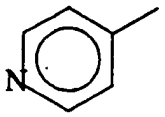


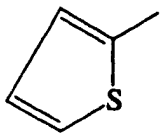
(I)

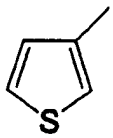
and pharmaceutically acceptable salts and stereoisomers thereof wherein

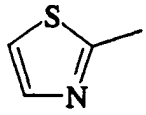
Ar^1 is an aryl moiety selected from the group consisting of:

(i)  ,

(ii)  ,

(iii)  ,

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of:

(i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

(ii) 2-, 4- or 5- thiazolyl,

(iii) 2-, 3- or 4-pyridinyl,

(iv) 2- or 3-thienyl, and

(v) 2- or 3-furyl;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

Y is selected from the group consisting of

(i) -O-,

(ii) -S-,

(iii) -NH-,

(iv) -S(O)-, and

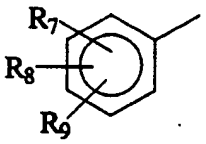
(v) $-S(O_2)-$;

R^1 is hydrogen, lower alkyl, lower alkoxy or cyclic alkyl;

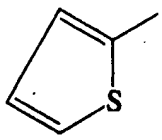
R^2 is lower alkyl or phenyl optionally substituted with lower alkyl or halogen or $NR^1(CH_2)$-$CONHSO_2R^2$ taken together forms pyrrolidino, piperidino, or piperazino substituted with $(CH_2)_p$-$CONHSO_2R^2$ and wherein the pyrrolidino, piperidino, or piperazino group is optionally substituted with one or two lower alkyl groups;

R_7, R_8, and R_9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2, NO_2 or OH;
m is an integer from 2 to 4;
n is an integer from 2 to 6; and
p is an integer from 1 to 3.

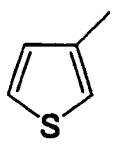
2. The compound of claim 1 wherein Ar^2 is chosen from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH.

3. The compound of claim 2 wherein Ar^1 has the structure: 

.

4. The compound of claim 2 wherein Ar^1 has the structure: 

.

5. The compound of claim 2 wherein Ar^1 has the structure: 

6. The compound of claims 3, 4 or 5 wherein Q is $-CH_2-$.

7. The compound of claim 6 wherein Y is -O-.

8. The compound of claim 7 wherein R^2 is lower alkyl

9. The compound of claim 7 wherein R^2 is chosen from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl wherein the subtitutents are chosen from the group consisting of alkyl and halogen.

10. The compound of claim 1 chosen from the group consisting of:

3-[Methyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(phenylsulfonyl)butanamide;

N-(Methylsulfonyl)-3-[methyl[3-[4-[(2-thienyl)-methyl]phenoxy]propyl]amino]propanamide;

3-[Ethyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide monohydrochloride;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrate;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(3-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

N-(methylsulfonyl)-3-[methyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

N-(phenylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide monohydrochloride;

N-(methylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

3-[(1-methylethyl[3-[4-[(3-thienyl)methyl]-phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[Cyclopropyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[(1,1-dimethylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

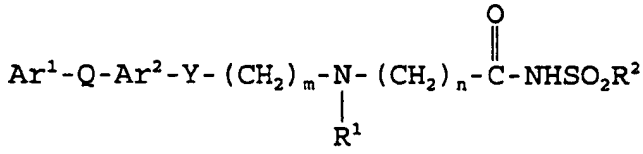
3-[(1-methylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[(1-methylethyl)[3-[4-[(phenylmethyl)-phenoxy]propyl]amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(phenylsulfonyl)-propanamide.

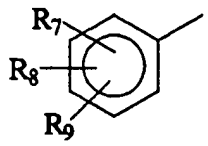
11. A pharmaceutical composition comprising a compound of the formula I:

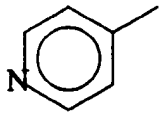


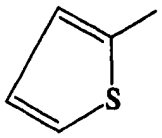
(I)

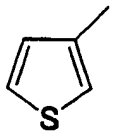
and pharmaceutically acceptable salts and stereoisomers thereof and a pharmaceutically acceptable carrier, wherein

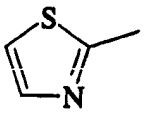
Ar^1 is an aryl moiety selected from the group consisting of:

(i)  ,

(ii)  ,

(iii) 

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of:

(i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

(ii) 2-, 4- or 5- thiazolyl,

(iii) 2-, 3- or 4-pyridinyl,

(iv) 2- or 3-thienyl, and

(v) 2- or 3-furyl;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

Y is selected from the group consisting of

(i) -O-,

(ii) -S-,

(iii) -NH-,

(iv) -S(O)-, and

(v) $-S(O_2)-$;

R^1 is hydrogen, lower alkyl, lower alkoxy or cyclic alkyl;

R^2 is lower alkyl or phenyl optionally substituted with lower alkyl or halogen or $NR^1(CH_2)$-$CONHSO_2R^2$ taken together forms pyrrolidino, piperidino, or piperazino substituted with $(CH_2)_p$-$CONHSO_2R^2$ and wherein the pyrrolidino, piperidino, or piperazino group is optionally substituted with one or two lower alkyl groups;

R_7, R_8, and R_9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2, NO_2 or OH;

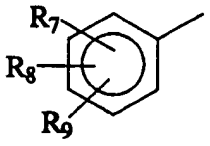
m is an integer from 2 to 4;

n is an integer from 2 to 6; and

p is an integer from 1 to 3.

12. The pharmaceutical composition of claim 11 wherein in the compound Ar^2 is is chosen from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH.

13. The pharmaceutical composition of claim 12 wherein

in the compound Ar^1 has the structure: 

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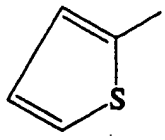
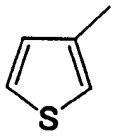
14. The pharmaceutical composition of claim 12 wherein in the compound Ar^1 has the structure:  .

15. The pharmaceutical composition of claim 12 wherein in the compound Ar^1 has the structure:

 .

16. The pharmaceutical composition of claims 13, 14 or 15 wherein in the compound Q is $-CH_2-$.

17. The pharmaceutical composition of claim 16 wherein in the compound Y is -O-.

18. The pharmaceutical composition of claim 17 wherein in the compound R^2 is lower alkyl

19. The pharmaceutical composition of claim 17 wherein in the compound R^2 is chosen from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl wherein the subtitutents are chosen from the group consisting of alkyl and halogen.

20. The pharmaceutical composition of claim 11 wherein the compound is chosen from the group consisting of:

3-[Methyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(phenylsulfonyl)butanamide;

N-(Methylsulfonyl)-3-[methyl[3-[4-[(2-thienyl)-methyl]phenoxy]propyl]amino]propanamide;

3-[Ethyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide monohydrochloride;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrate;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(3-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

N-(methylsulfonyl)-3-[methyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

N-(phenylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide monohydrochloride;

N-(methylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

3-[(1-methylethyl[3-[4-[(3-thienyl)methyl]-phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[Cyclopropyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[(1,1-dimethylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[(1-methylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

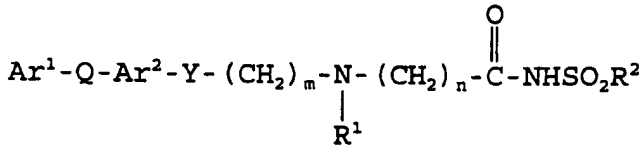
3-[(1-methylethyl)[3-[4-[(phenylmethyl)-phenoxy]propyl]amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(phenylsulfonyl)-propanamide.

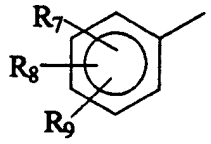
21. A method for treating an LTB_4-mediated inflammatory disease comprising administering to a

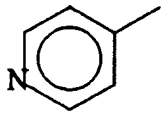
mammal in need of treatment a therapeutically effective amount of a compound of the formula I:

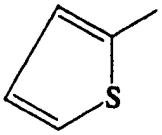


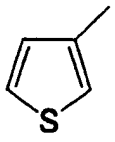
and pharmaceutically acceptable salts and stereoisomers thereof wherein

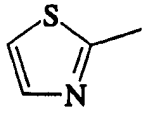
Ar^1 is an aryl moiety selected from the group consisting of:

(i)  ,

(ii)  ,

(iii)  ,

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of:

(i) phenyl, mono-, di-, or tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

(ii) 2-, 4- or 5- thiazolyl,

(iii) 2-, 3- or 4-pyridinyl,

(iv) 2- or 3-thienyl, and

(v) 2- or 3-furyl;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

Y is selected from the group consisting of

(i) -O-,

(ii) -S-,

(iii) -NH-,

(iv) -S(O)-, and

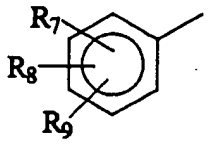
(v) $-S(O_2)-$;

R^1 is hydrogen, lower alkyl, lower alkoxy or cyclic alkyl;

R^2 is lower alkyl or phenyl optionally substituted with lower alkyl or halogen or $NR^1(CH_2)$-$CONHSO_2R^2$ taken together forms pyrrolidino, piperidino, or piperazino substituted with $(CH_2)_p$-$CONHSO_2R^2$ and wherein the pyrrolidino, piperidino, or piperazino group is optionally substituted with one or two lower alkyl groups;

R_7, R_8, and R_9 are independently H, halogen, lower alkyl, lower alkoxy, NH_2, NO_2 or OH;
m is an integer from 2 to 4;
n is an integer from 2 to 6; and
p is an integer from 1 to 3.

22. The method of claim 21 wherein in the compound Ar^2 is chosen from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl with the substituents selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH.

23. The method of claim 22 wherein in the compound Ar^1 has the structure: 

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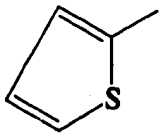
24. The method of claim 22 wherein in the compound Ar^1 has the structure: 

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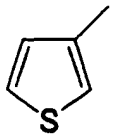
25. The method of claim 22 wherein in the compound Ar^1 has the structure: 

.

26. The method of claims 23, 24 or 25 wherein in the compound Q is $-CH_2-$.

27. The method of claim 26 wherein in the compound Y is -O-.

28. The method of claim 27 wherein in the compound R^2 is lower alkyl.

29. The method of claim 27 wherein in the compound R^2 is chosen from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl wherein the subtitutents are chosen from the group consisting of alkyl and halogen.

30. The method of claim 21 wherein the compound is chosen from the group consisting of:
3-[Methyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(phenylsulfonyl)butanamide;

N-(Methylsulfonyl)-3-[methyl[3-[4-[(2-thienyl)-methyl]phenoxy]propyl]amino]propanamide;

3-[Ethyl[3-[4-[(2-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(2-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide monohydrochloride;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrate;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

3-[(1-methylethyl) [3-[4-[(3-thienyl)methyl]-phenoxy]propyl]amino]-N-(phenylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide monohydrochloride;

N-(methylsulfonyl)-3-[methyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

N-(phenylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide monohydrochloride;

N-(methylsulfonyl)-3-[propyl[3-[4-[(3-thienyl)methyl]phenoxy]propyl]-amino]propanamide;

3-[(1-methylethyl[3-[4-[(3-thienyl)methyl]-phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(phenylsulfonyl)propanamide;

3-[Methyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[Cyclopropyl[3-[4-[(3-phenylmethyl)phenoxy]propyl]-amino]-N-(methylsulfonyl)propanamide;

3-[(1,1-dimethylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[(1-methylethyl)[3-[4-[(3-phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[(1-methylethyl)[3-[4-[(phenylmethyl)-phenoxy]propyl]amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(methylsulfonyl)-propanamide;

3-[Ethyl[3-[4-[(phenylmethyl)-phenoxy]propyl]-amino]-N-(phenylsulfonyl)-propanamide.

INTERNATIONAL SEARCH REPORT

In. .ational Application No
PCT/US 98/03928

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/62 C07D333/16 C07C311/18 C07C311/51 A61K31/38 A61K31/18

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and. where practical. search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document. with indication. where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 11192 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 see the whole document ---	1-20
Y	WO 96 10999 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 see the whole document ---	1-20
Y	DE 41 21 849 A (RHONE POULENC RORER GMBH) 14 January 1993 see the whole document ---	1-20
X	WO 96 41625 A (SEARLE & CO) 27 December 1996 see the whole document ---	11
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
22 June 1998	09. 07. 98

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intl. ..ional Application No
PCT/US 98/03928

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 117, no. 11, 14 September 1992 Columbus, Ohio, US; abstract no. 111411, XP002068845 see abstract & R. LABAUDINIÈRE ET AL.: J. MED. CHEM., vol. 35, no. 17, 1992, pages 3156-3169, ---	1-20
A	CHEMICAL ABSTRACTS, vol. 126, no. 1, 1 January 1997 Columbus, Ohio, US; abstract no. 302, XP002068846 see abstract & J.H. YUAN ET AL.: DRUG METAB. DISPOS. , vol. 24, no. 10, 1996, pages 1124-1133, -----	1-20

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INTERNATIONAL SEARCH REPORT

I· national application No.
PCT/US 98/ 03928

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21-30
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 21-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and the compounds mentioned in the claims. (see Guidelines, Chapter III, paragraph 2.3).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/03928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9611192 A	18-04-1996	US 5585492 A	17-12-1996
		AU 3686595 A	02-05-1996
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		EP 0804427 A	05-11-1997
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		EP 0843549 A	27-05-1998